Four Cases of Thrombotic Events Associated with Neuro-Endovascular Therapy: Heparin Resistance and Aspirin Resistance

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Summary

Thrombotic events are caused by insufficient antithrombotic treatment in endovascular surgery. We experienced four cases of thrombotic events and consider the factors from the point of view of heparin resistance and aspirin resistance. The proportion of these features is quite high and appropriate management is important.

Introduction

At our institute, in the coil embolization of unruptured cerebral aneurysms and carotid stenting, all patients are systemically received antithrombotic treatment with pre- and post-operative internal use of aspirin and intra-venous (IV) administered doses of the heparin to achieve prolongation of activated clotting time (ACT) to twice baseline on the operating table and for one day postoperatively. We report four cases of thrombotic events in endovascular surgery and consider the factors in the light of antithrombotic treatment, especially from the point of view of heparin resistance and aspirin resistance.

Case report

Case 1 (figure 1): A 63-year-old man, body weight 62 kg, underwent coil embolization for unruptured left internal carotid-posterior communicating (IC-PC) aneurysm. Anti-platelet drug (ticlopidine 200 mg) was administered for two weeks before treatment.

Heparin 5000U were administered before the first coil delivered. ACT was not tested during procedure. After coil embolization, angiography showed the occlusion of left posterior communicating artery (PCOM) and following posterior cerebral artery (PCA). It was thought to be brought by the thrombosis around the coil. Intravenous bolus of heparin (2000U) was added and thrombolytic therapy was tried. But recanalization was not obtained. After transference to the intensive care unit, ACT was tested. It was 134 s, not sufficiently prolonged. Heparin resistance was thought to be exist in this patient. Decrease in circulating antithrombin III (AT III), its activity was 52%, was recognized. High dose heparin was needed to achieve enough prolongation of ACT.

Case 2 (figure 2): A 56-year-old woman, body weight 48 kg, underwent coil embolization for unruptured basilar top aneurysm. Anti-platelet drug (aspirin 400 mg) was administered for two weeks before treatment. Baseline ACT was 102 s. After the placement of femoral sheath, repeat boluses of heparin (total 10000U) were administered. But ACT prolonged so far as to 183 s, not achieved to twice baseline.

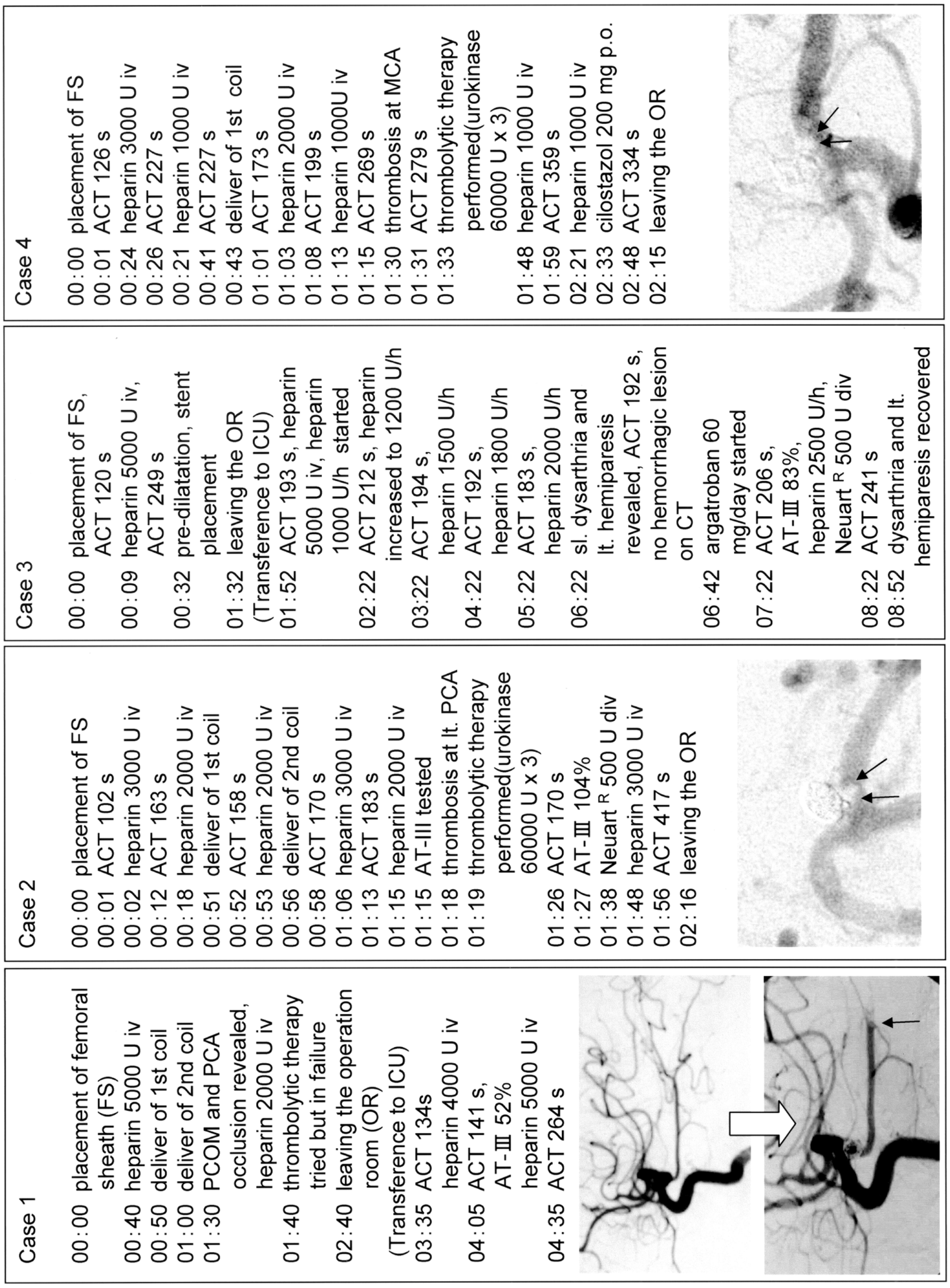

Figure 1 Surgical courses. Case 1 insert: an arrow indicates the occlusion of left PCA. Case 2 insert: arrows indicate the thrombosis at left PCA. Case 4 insert: arrows indicate the thrombosis at left MCA.

The procedure was still continued under this situation as it was. Later angiography showed the thrombosis at left PCA adjacent to inferior margin of the cage. Thrombolytic therapy was performed, but complete disappearance of thrombus was not obtained. Even at this time, ACT was 170 s. Enough prolongation of ACT was not secured, so heparin resistance was thought to be exist in this patient. Although decrease in circulating AT III was not recognized, its activity was 104%. After purified AT III concentrate (Neuart® 500U) was received, ACT prolonged rapidly to 417 s and thrombus disappeared.

Case 3 (figure 3): A 79-year-old man, body weight 68 kg, underwent carotid artery stenting (CAS) for right carotid artery stenosis. Antiplatelet drug (aspirin 200 mg and cilostazol 200 mg) was administered before treatment. Baseline ACT was 120 s. After inhtravenous bolus of heparin (5000U), ACT prolonged to 249 s >2 times baseline.

The procedure was completed with no complication. After leaving the operation room, systemic heparinization was continued. In spite of gradual increase of infusion dose, enough prolongation of ACT was not secured.

Five hours after the procedure, she revealed slight dysarthria and left upper and lower limbs weakness. Brain CT showed no hemorrhagic lesion. The possibility was thought of thrombosis caused by insufficient anticoagulation. The administration of argatroban (60 mg/day) and purified AT III concentrate (Neuart® 500U) was begun. Subsequently ACT prolonged to 241 s and her neurodeficit took a turn for the recovery.

Case 4 (figure 4): A 78-year-old woman, body weight 42 kg, underwent unruptured internal carotid bifurcation aneurysm.

In consideration of her anamnesis of ticlopidine-induced liver dysfunction, only aspirin 200 mg was administered before treatment. Baseline ACT was 126 s. After intravenous bolus of heparin (3000U), ACT prolonged to 227 s. Repeat boluses of heparin were administered to maintain the ACT at >twice baseline, but angiography showed the thrombosis at left middle cerebral artery (MCA) adjacent to inferior margin of the cage.

At this time, ACT was 279 s. Thrombolytic therapy was performed.

Sufficient anticoagulation was secured, so the possibility was thought of insufficient inhibition of platelet function result from low aspirin doses of 200 mg. After immediate administration of cilostazol 200 mg, thrombosis was not recognized.

Discussion

In cases 1, 2 and 3, thrombotic events are thought to be caused by insufficient anticoagulation. For the cause of anticoagulation failure, heparin resistance (HR) is a common (10-20%) feature in cardiopulmonary bypass [1,2]. HR is diagnosed in the case of failure to reach an ACT longer than 480 s after an intravenous bolus administration of 300U/kg heparin or heparin sensitivity index (HSI) [3], derived from the formula: (ACT after heparin - ACT baseline) / heparin loading dose (U/kg), below 1.0. From a previous paper analysis, A deficiency of circulating AT III (its activity 60% ≥) is responsible for a 60% risk of HR [1]. In case 1, HSI was unidentified but AT III activity was 52% (<60), the existence of HR is expected. In case 2, HSI was 0.6 (<1.0), it satisfies the criteria of HR. In case 3, HSI was 1.7 (>1.0), it can not be made a diagnosis of HR.

Concerning the treatment of HR, M Ranucci et Al recommend the following way in their paper [4] that, all patients with a baseline AT III activity <70% should routinely receive purified AT III concentrates, patients with AT III activity between 70% and 100%, if they manifest a HR pattern after the heparin loading dose, should be tested with a further heparin dose, but, if they fail to reach an adequate ACT, they should receive purified AT III concentrates. In our field of endvascular therapy, we should wait for the procedure until adequate ACT is secured. As for the patients manifest a HR pattern, we should consider the use of purified AT III concentrates.

In case 4, the existence of aspirin resistance is expected. Although formal diagnostic criteria are lacking, the term "aspirin resistance" is generally used to describe the inability of aspirin to protect individuals from thrombotic complications, or to produce an anticipated effect on one or more in vitro tests of platelet function [5]. In a previous paper from Japan [6], it is reported that the proportion of aspirin resistance was 38% with 324 mg aspirin. In the same study, as-

pirin inhibited platelet aggregation in a dose-dependent manner.

Buchanan and Brister reported that most aspirin nonresponders tested with low doses of aspirin were responders at high doses (1300 mg aspirin)[7].

In the management of those patient who are aspirin resistant, Laszlo KS et Al recommend an increase in dosage of aspirin or another antiplatelet drug plus aspirin[8].

Conclusions

Thrombotic events are caused by insufficient antithrombotic treatment in endovascular surgery. For the cause of this situation, heparin resistance and aspirin resistance are important. We should perform the procedure with these features in mind, and when the thrombotic events occur, appropriate management is implemented.

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